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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,097	01/28/2004	Francois Lang	BECK1170-1	9827

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
04/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,097	LANG ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/12/07, 11/17/07, 12/19/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14 and 16-35* is/are pending in the application.

4a) Of the above claim(s) *17,18,21-26,29 and 32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,16,19, 20, 27,28,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 7/12/07 and Applicant's responses filed 11/1/7/07 and 12/19/08 are acknowledged and have been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I and species of MHC class I tetramer wherein at least one amino acid substitution in the α3 domain of the heavy chain in the zone of interaction with CD8 is mutated in Applicant's response filed 12/18/06.

3. Applicant's election without traverse of α3 domain mutation of A245V in HLA-A2 in Applicant's response filed 11/7/07, Applicant's election without traverse of multimer comprising a fluorescent molecule, A245V α3 domain mutation in HLA-A2 and no antigenic peptide loaded in the multimers in Applicant's response filed 2/19/08, and Applicant's election with traverse of soluble multimers in Applicant's response filed 2/19/08 is acknowledged.

The basis for Applicant's traversal is of record in the response filed 1/19/08 on pages 2-6.

Upon reconsideration, the Examiner will consider Applicant's election of "soluble" instead as "not bound to a streptavidin-coupled bead."

Claims 14, 16, 27, 30 and 31 read on the elected species.

Accordingly, claims 19 and 20 are presently a non-elected species of elected Group I pursuant to Applicant's election of "no peptide loaded in the multimers" in Applicant's response filed 2/19/08, however, based upon the prior art, examination has been extended to include peptide-loaded multimers recited in claims 19 and 20. In addition, upon consideration of the prior art, the species of multimer recited in instant claim 28, *i.e.*, "further comprising a biotin molecule" is also being examined.

Claims 14, 16, 19, 20, 27, 28, 30 and 31 are presently being examined.

With regard to Applicant's request for rejoinder of all species claims in elected Group I if the elected species claims are found allowable, Applicant is reminded that the Examiner would move on to examine another species, not all species.

4. Applicant is reminded that the amendment filed 1/28/04 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The incorporation by reference of PCT/FR00/02443 because the preliminary amendment was not mentioned in the declaration (filed in the 09/831,019 parent application). Applicant is required to cancel the new matter in the reply to this Office Action.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 14, 16, 19, 20, 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

This new ground of rejection is necessitated by Applicant's amendment filed 7/12/07.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed MHC class I analogue multimer recited in base claim 14, and including those recited in the dependent claims, said multimer characterized in that the MHC class I analogue proteins comprise at least one modification in the $\alpha 3$ zone of interaction of a heavy chain with the CD8 co-receptor leading to a reduction of the affinity of the interaction between the heavy chain and CD8.

Applicant is claiming a broad genus of $\alpha 3$ domain modified MHC class I multimers with reduced affinity of binding to CD8. The instant claims encompass tetramers of MHC class I, as well as lower and higher order multimers of MHC class I, wherein a modification, including a mutation, is made in at least one of the $\alpha 3$ domain amino acid residues of the MHC class I heavy chain that interacts with CD8, such that there is a reduction of the affinity of interaction between the heavy chain and CD8. In addition, the limitation "modification" also encompasses a substitution, truncation, deletion, chemical alteration, addition of amino acid residues. There is insufficient disclosure in the specification of said multimer using said exogenous compound.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3). The specification discloses that an example of a mutation in the α3 domain of the heavy chain is A245V (page 5 at lines 16-18). Applicant's disclosure is to a method for using the claimed multimer to detect CD8+ T lymphocytes specific for a particular MHC class I/peptide complex while reducing non-specific detection due to the ability of CD8 to bind to class I MHC molecules (especially page 2 at the full paragraph), the multimer exemplified being the aforementioned A245 mutant.

Evidentiary reference Gao *et al* (Nature. 1997, 387(6633): 630-634, of record) teach that CD8$\alpha\alpha$ binds one HLA-A2/peptide molecule, interfacing with the α2 and α3 domains of HLA-A2 and also contacting β2m. A flexible loop of the α3 domain (residues 223-229) is damped between the complementarity determining region-like loops of the two CD8 subunits in the classic manner of an antibody-antigen interaction, precluding the binding of a second MHC molecule. The position of the α3 domain is different from that in uncomplexed HLA-A2, but no conformational change extends to the MHC /peptide surface presented for TCR recognition. Thus, the said reference teaches that other domains of heavy chain other than the α3 domain as well as β2m light chain interact with CD8. Gao *et al* further teach that one human allele, HLA-Aw68, has been reported to show an aberrantly low level of CD8 binding, and effect that has been linked to polymorphism at residue 245 (A245V, the same mutation disclosed as the working example in the instant specification). Gao *et al* teach that although there is no direct contact between CD8aa and residue 245, mutation of this residue in HLA-Aw68 leads to significant distortion of the 223-229 loop from the conformation seen in all other structurally characterized alleles and required for binding to CD8 (especially abstract and paragraph spanning columns 1 and 2 on page 632).

Although the skilled artisan was aware that amino acid residues in the α3 domain along with other amino acid residues in the α2 domain and in the β2m light chain contact CD8$\alpha\alpha$, the instant specification does not disclose what α3 domain modification(s) are sufficient by itself/themselves to confer the property of reducing the CD8/heavy chain affinity of interaction at all and including without loss of said affinity. The mutation in Applicant's sole working example A245V results in a distortion of the 223-229 loop from the conformation typically seen in structurally characterized HLA alleles except for HLA-Aw68. Applicant's claimed invention is not drawn to a method for determining what modification(s) may be made in the α3 domain of a MHC class I molecule that leads to a reduction of the affinity of the interaction between the MHC class I heavy chain and

CD8, but is rather drawn to a multimer of such an MHC class I analogue. "Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features." See University of Rochester, 358 f.3d at 927, 69 USPQ2d at 1895.

One of skill in the art would not have recognized that Applicant was in possession of the necessary common attributes or features possessed by the members of the genus.

7. Applicant's amendment filed 7/12/07 has overcome the prior rejection of record of claims 14, 16 and 27 under 35 U.S.C. 112, first paragraph.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Applicant's amendment filed 7/12/07 has overcome the prior rejection of record under 35 U.S.C. 102(a) based upon Bodinier *et al* (Nature Medicine. 6/00, 6(6): 707-710. Applicant has filed a certified translation of the FR 9911133 foreign priority document.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 14, 16, 19, 20, 27, 28, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao *et al* (Nature. 1997, 387(6633): 630-634) in view of Ogg and McMichael (Curr. Opin. Immunol. 1998, 10: 393-396).

Applicant's amendment filed 7/12/07 has necessitated this new ground of rejection.

Gao *et al* teach that one human allele, HLA-Aw68, has been reported to show an aberrantly low level of CD8 binding, and effect that has been linked to polymorphism at residue 245 (*i.e.*, A245V). Gao *et al* teach that although there is no direct contact between CD8$\alpha\alpha$ and residue 245, mutation of this residue in HLA-Aw68 leads to significant distortion of the 223-229 loop from the conformation seen in all other structurally characterized alleles and required for binding to CD8 (especially abstract and paragraph spanning columns 1 and 2 on page 632).

Gao *et al* do not teach HLA-Aw68 tetramers.

Ogg and McMichael teach HLA-peptide tetramers, wherein the HLA heavy chain comprises a biotin molecule, and their use for direct *ex vivo* visualization of antigen specific CD8+ T cells and NK cells by flow cytometry. Ogg and McMichael teach labeling the tetramers with a fluorescent compound (see entire reference).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made tetramers as taught by Ogg and McMichael using the HLA-Aw68 molecule taught by Gao *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a reagent that can be used to directly visualize antigen specific CD8+ T cells and NK cells.

With regard to the limitation recited in base claim 14, *i.e.*,"a multimer of recombinant protein analogues of class I MHC", the HLA-Aw68 class I molecule is an analogue of all other structurally characterized alleles as taught by Gao *et al*, the instant base claim 14 also recites "characterized in that the proteins comprise", and the art HLA-Aw68 protein meets the recited structural claim limitations that it comprises a modification in the a3 domain (A245V) relative to other class I MHC proteins that leads to a reduction of the affinity of the interaction between the heavy chain and CD8 relative to the other class I MHC proteins.

12. Claims 14, 16, 19, 20, 27, 28, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Missale *et al* (J. Exp. Med. 1993, 177: 751-762) in view of Ogg and McMichael (Curr. Opin. Immunol. 1998, 10: 393-396).

Applicant's amendment filed 7/12/07 has necessitated this new ground of rejection.

Missale *et al* teach HLA-Aw68-restricted CTL responses to three HBV viral peptide epitopes and monitoring HBV-CTL responses (see entire reference, especially abstract).

Missale *et al* do not teach HLA-Aw68 tetramers.

Ogg and McMichael teach HLA-peptide tetramers, wherein the HLA heavy chain comprises a biotin molecule, and their use for direct *ex vivo* visualization of antigen specific CD8+ T cells and NK cells by flow cytometry. Ogg and McMichael teach labeling the tetramers with a fluorescent compound (see entire reference).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made tetramers as taught by Ogg and McMichael using the HLA-Aw68 molecule taught by Missale *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a reagent that can be used to directly visualize antigen specific CD8+ T cells and NK cells.

With regard to the limitation recited in base claim 14, *i.e.*,"a multimer of recombinant protein analogues of class I MHC", the HLA-Aw68 class I molecule is an analogue of all other structurally characterized alleles as taught by Gao *et al*, the instant base claim 14 also recites "characterized in that the proteins comprise", and the art HLA-Aw68 protein meets the recited structural claim limitations that it comprises a modification in the a3 domain (A245V) relative to other class I MHC proteins that leads to a reduction of the affinity of the interaction between the heavy chain and CD8 relative to the other class I MHC proteins.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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March 26, 2009

/G.R. Ewoldt/
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